Title
Level of Exercise Influences the Severity of Fatigue, Energy Levels, and Sleep Disturbance in Oncology Outpatients Receiving Chemotherapy

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Level of Exercise Influences the Severity of Fatigue, Energy Levels, and Sleep Disturbance in Oncology Outpatients Receiving Chemotherapy

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DEDICATION AND ACKNOWLEDGMENTS

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Level of Exercise Influences the Severity of Fatigue, Energy Levels, and Sleep Disturbance in Oncology Outpatients Receiving Chemotherapy, Sally Moy, Abstract

Background – Fatigue and sleep disturbance are common co-occurring symptoms in patients receiving chemotherapy (CTX). While the results from the meta-analyses support the use of exercise to decrease the severity of these symptoms, information is needed on patients' "real world experiences" with the use of exercise during CTX.

Objective – Determine the distribution of patients who did and did not exercise on a regular basis and evaluate for differences in demographic and clinical characteristics, as well as the severity of fatigue, decrements in energy, and sleep disturbance among the exercise groups.

Methods – Patients (n=1033) completed self-report questionnaires prior to their second or third cycle of CTX. Patients were categorized into 3 exercise (Ex) groups (i.e., NoEx, <150 minutes/week (LessEx), ≥150 minutes/week (RecEx). Differences among the groups were evaluated using parametric and nonparametric tests.

Results – Only 19.1% of the patients were in the RecEx group. Patients in the NoEx group (37.2%) were had fewer years of education, were more likely to be non-white and unemployed, had a higher BMI and a worse comorbidity profile. Patients in the NoEx group had higher levels of morning fatigue, lower levels of morning and evening energy, and higher levels of sleep disturbance.

Conclusions – Findings from this "real world" study suggest that lack of physical activity is associated with higher levels of fatigue and sleep disturbance.

Implications for Practice – Given that the most frequently used intervention in this study was walking, clinicians can recommend this inexpensive intervention to patients to manage fatigue and sleep disturbance.

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LIST OF ABBREVIATIONS

AUDIT: ALCOHOL USE DISORDERS IDENTIFICATION TEST

CTX: CHEMOTHERAPY

dl: DECILITER

Ex: EXERCISE

GSDS: GENERAL SLEEP DISTURBANCE SCALE

LessEx: GROUP WITH REGULAR EXERCISE BUT LESS THAN RECOMMENDED AMOUNT

LFS: LEE FATIGUE SCALE

m^2: METER SQUARED

MIN: MINUTES

n: SAMPLE SIZE

NS: NOT SIGNIFICANT

KG: KILOGRAM

KPS: KARNOFSKY PERFORMANCE STATUS

NoEx: GROUP WITHOUT REGULAR EXERCISE

NRS: NUMERIC RATING SCALE

RecEx: GROUP WITH REGULAR EXERCISE AT OR EXCEEDING RECOMMENDED AMOUNT

RT: RADIATION THERAPY

SCQ: SELF-ADMINISTERED COMORBIDITY QUESTIONNAIRE

SD: STANDARD DEVIATION

INTRODUCTION

Over 50% of oncology patients will receive surgery and chemotherapy (CTX) to treat their cancer.[1] Fatigue is one of the most common and distressing symptoms that occurs in 70% to 100% of patients receiving CTX.[2] Cancer-related fatigue is defined as a “distressing, persistent, subjective sense of physical, emotional, or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”.[3] As outlined in several reviews,[4-6] the underlying mechanisms for fatigue are multifactorial and include: immune activation and inflammation, activation of the hypothalamic-pituitary-adrenal axis, metabolic and/or endocrine dysfunction, disruption in circadian rhythms, and abnormalities in neuromuscular function.

An equally common and problematic symptom in patients receiving CTX is sleep disturbance. While not routinely assessed, occurrence rates for sleep disturbance range from 30% to 60%.[7, 8] In one study of patients receiving CTX,[9] prevalence rates for sleep disturbance were three times higher than in the general population. Similar to fatigue, the underlying mechanisms for sleep disturbance in oncology patients are multifactorial and not completely understood. As noted in one review,[10] the cancer itself as well as the receipt of CTX induces systemic inflammation as well as disruptions in metabolic and endocrine functions that can have a negative effect on sleep neurocircuitry.

Emerging evidence suggests that fatigue and sleep disturbance co-occur in oncology patients [11, 12] because they share common underlying mechanisms.[13] Across several studies, our research team reported that higher levels of fatigue prior to the initiation of radiation therapy,[14] prior to surgery for breast cancer,[15] and prior to CTX [16] were associated with higher levels of sleep disturbance over time. Similar associations were found when fatigue was the dependent variable in the longitudinal analyses (i.e., higher levels of sleep disturbance predicted higher levels of fatigue over time [17-21]). Despite the high occurrence rates, relative

inter-relatedness, and detrimental effects of both symptoms on oncology patients' functional status and quality of life (QOL), effective treatments for both symptoms are lacking.

A growing body of evidence suggests that exercise is a cost effective intervention to decrease the incidence of cancer and inhibit tumor growth.[22-25] While the mechanisms that underlie the efficacy of exercise are not well understood, current data suggest that exercise may effect tumor growth through the mobilization and activation of cytotoxic immune cells and regulation of acute and chronic systemic inflammatory responses.[23] Given that an alteration in inflammatory responses associated with the administration of CTX is one of the hypothesized mechanisms for both fatigue and sleep disturbance, a number of randomized clinical trials have evaluated the efficacy of exercise for these symptoms. In terms of fatigue, across several systematic reviews and meta-analyses of patients undergoing active treatment as well as cancer survivors,[26-34] the findings suggest that multimodal exercise interventions that include aerobic, resistance, and stretching exercises are effective in decreasing fatigue. While less well studied and often evaluated as a secondary outcome,[35-38] findings from four systematic reviews suggest that regular exercise results in decreases in sleep disturbance.

While the results from the meta-analyses cited above support the use of exercise to decrease fatigue and sleep disturbance in oncology patients undergoing CTX, information is needed on patients' "real world experiences" with the use of exercise and its association with symptom severity. Five studies were identified that used self-report measures to evaluate levels of exercise in oncology patients undergoing cancer treatment.[39-43] Across these five studies, between 7% [40] and 55.9% [42] reported that they did not engage in routine physical activity. While in one study, fatigue was found to be a significant barrier to regular exercise,[40] only one study evaluated the relationships between exercise and the severity of fatigue and sleep disturbance in women (n=119) with breast, ovarian, or colorectal cancer prior to their second dose of CTX. [42] While no differences in sleep disturbance scores were found between the exercisers and non-exercisers, lower fatigue scores were reported by the exercise group at

enrollment. Given the paucity of “real world data” on the relationships between exercise and fatigue and sleep disturbance, the purposes of this study in a sample of patients undergoing CTX (n = 1033) were to: determine the distribution of patients who did and did not exercise on a regular basis using the recommendation for physical activity from the Office of Disease Prevention and Health Promotion’s Healthy People 2020 report (i.e., ≥150 minutes of exercise per week) [44]; evaluate for differences in demographic and clinical characteristics among the exercise groups; and evaluate for differences in the severity of fatigue, decrements in energy, and sleep disturbance among the exercise groups.

METHODS

Patients and settings

This analysis is part of a longitudinal study that evaluated the symptom experience of oncology outpatients receiving CTX. Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran’s Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment.

Evaluation of regular exercise

Patients (n=1033) completed a 6-item exercise questionnaire that asked them whether or not they exercised on a regular basis; what types of physical activity they engaged in at the present time (e.g., walk, swim); how many days per week they exercised; how many times per day they exercised; as well as the duration and intensity of each session. Based on responses to this questionnaire, three exercise groups were created: patients who did not exercise on a

regular basis (NoEx); patients who exercised <150 minutes per week (LessEx); and patients who exercised for the recommended ≥150 minutes per week (RecEx). [44]

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, patients completed the Karnofsky Performance Status (KPS) scale)[45] and the Self-Administered Comorbidity Questionnaire (SCQ.[46]

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy.[47] Each item was rated on a 0 to 10 numeric rating scale (NRS). Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaires, patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cutoff scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) [48] and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy).[48] The LFS has well established validity and reliability.[47, 49] In the current study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess the quality of sleep. Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the seven subscale scores that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicate higher levels of sleep disturbance. Subscales scores of ≥3 and a GSDS total score of ≥43 indicate a significant level of sleep disturbance.[48] The GSDS has well established validity and reliability.[49-51] In the current study, the Cronbach's alpha for the GSDS total score was 0.83.

Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Eligible patients were approached by a research staff member in the infusion unit during their first or second cycle of CTX to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles, patients completed questionnaires in their homes, a total of six times over two cycles of CTX. For this analysis, symptom data from the enrollment assessment, that asked patients to report on their symptom experience for the week prior to the administration of their next cycle of CTX, were analyzed (i.e., recovery from previous CTX cycle). Medical records were reviewed for disease and treatment information.

Data analysis

Data were analyzed using SPSS version 25 (IBM, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic, clinical, and symptom characteristics. The three exercise groups were created using the patients' responses to the exercise questionnaire. Patients who responded no to the question about whether or not they exercised on a regular basis were assigned to the NoEX group. The remaining two groups were assigned based on a calculation of the number of times they exercised per week, the number of times per day that they exercised, and the duration of the exercise sessions. Differences among the three exercise groups in demographic and clinical characteristics, as well symptom severity scores, were evaluated using analysis of variance, Chi square analyses, or Kruskal-Wallis tests. A p-value of $<.05$ was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of $<.017$ (.05/3 pairwise comparisons).

RESULTS

Classification of the exercise groups

Of the 1033 patients who completed the exercise questionnaire, 37.2% were classified in the NoEx group, 43.7% in the LessEx group, and 19.1% in the RecEx group. As shown in Figures 1A to ID, compared to the RecEx group, patients in the LessEx group, exercised for fewer minutes per session as well as for fewer total minutes per week and participated in less intense exercise and for fewer days per week (all, p<.001) Differences between the two groups in the types of exercise are illustrated in Figure 2.

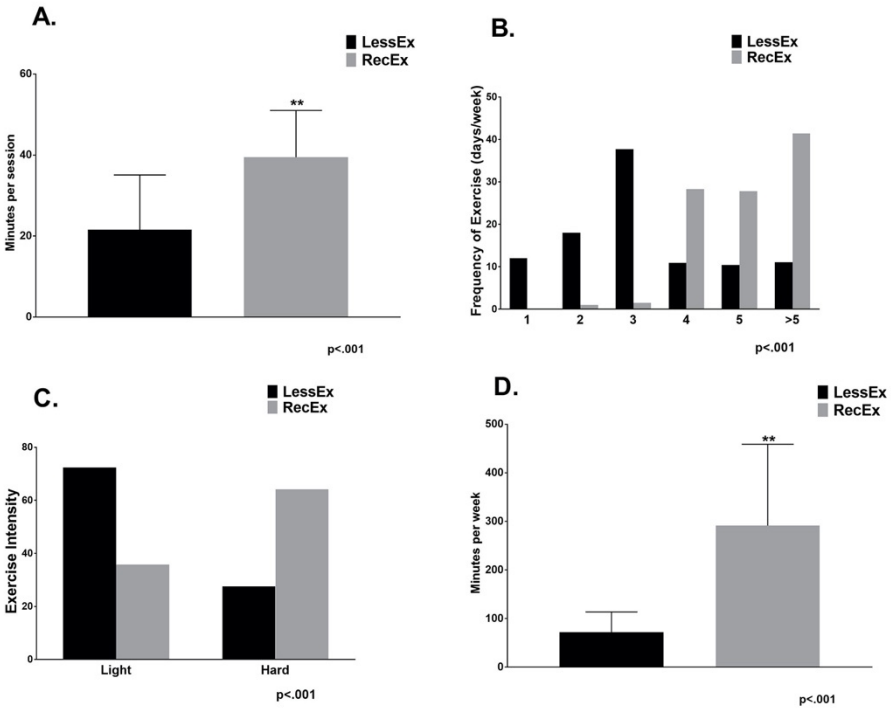

Figure 1: (A) Comparison of minutes per exercise session in LessEx vs. RecEx. (B) Comparison of frequency of exercise sessions in LessEx vs. RecEx. (C) Comparison of exercise intensity in LessEx vs. RecEx. (D) Comparison of minutes of exercise per week in LessEx vs. RecEx.

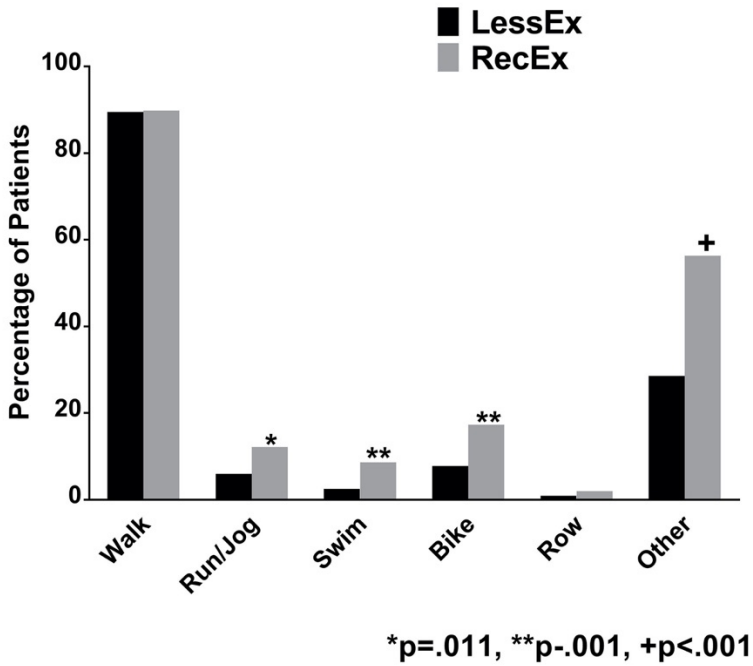

Figure 2: Comparison of types of exercise undertaken by LessEx vs. RecEx patients.

Differences in demographic and clinical characteristics

In terms of demographic characteristics, statistically significant differences were found among the three exercise groups in level of education (NoEx < Less Ex < RecEx). In addition, compared to the RecEx group, patients in the NoEx group were more likely to be Nonwhite and less likely to be employed. Compared to the RecEx group, patients in the other two groups reported a lower annual household income.

In terms of clinical characteristics, statistically significant differences were found among the three exercise groups in body mass index (BMI; NoEx > LessEx > RecEx) and KPS score (NoEx < LessEx < RecEx). Compared to the other two exercise groups, patients in the NoEx group had a higher number of comorbidities, a higher SCQ score, were more likely to have high blood pressure, and were less likely to have breast cancer than the other cancer diagnoses. Compared to the RecEx group, patients in the other two exercise groups were more likely to report diabetes and back pain.

Differences in fatigue and energy

While no significant differences were found in evening fatigue among the three exercise groups, compared to the other two groups, patients in the NoEx group had significantly higher levels of morning fatigue. In terms of morning energy, statistically significant differences were found among the three groups (NoEx < Less Ex < RecEx). In terms of evening energy, compared to the RecEx group, patients in the NoEx group reported significantly lower energy levels (Table 2).

Differences in sleep disturbance

No differences were found among the three exercise groups in the GSDS subscale scores for: quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, and medication for sleep. Compared to the RecEx group, patients in the NoEx group reported significantly higher scores for quality of sleep (which indicates poorer sleep quality) and overall level of sleep disturbance.

DISCUSSION

This large “real world” study of oncology patients receiving CTX is the first to evaluate for differences in the severity of fatigue, decrements in energy, and sleep disturbance based on self-reported levels of exercise. Only 19% of patients in our study were categorized as meeting the Healthy People 2020 guideline recommendation to exercise for ≥150 min/week. This percentage is higher than the 7% found in a Danish study of patients undergoing CTX [40] but lower than the 55.9% reported by women with breast, colorectal, and ovarian cancer who were beginning their first cycle of CTX.[42] A comparison of findings across studies is challenging due to heterogeneity in cancer diagnoses and treatment regimens, the methods used to assess physical activity, as well as the timing of the measures in relationship to cancer treatments. In terms of the general population of the United States, less than 5% of adults participate in 30 minutes of physical activity each day and only one in three meet the recommended amount of physical activity each week.[52]

Ethnicity was one of the demographic characteristics associated with reporting lower levels of exercise. Consistent with studies of the general population,[53, 54] Nonwhites were more likely to be in the NoEx or LessEx groups. These differences may occur because of the higher likelihood that members of ethnic minority groups may have decreased access to safe public parks and recreational facilities in their neighborhoods. In addition, these individuals are more likely to have physically demanding jobs with work hours that reduce their opportunities to engage in more physically active leisure activities.[53, 55-58]

Years of education was another demographic characteristic that differentiated among the three exercise groups, with patients in the NoEx group having the fewest years of education. Again, this finding is consistent with trends in the general population,[59, 60] as well as with a number of intervention studies that found that oncology patients with more education had higher rates of adherence with prescribed exercise regimens.[61-63] The complex relationship between education and health, often referred to as an education gradient, is partially explained by the idea that individuals with more years of education have higher incomes that provide increased access to resources (e.g., gym memberships); afford more time for health-related activities; and provide access to social networks that can amplify health behaviors like exercise.[60, 64, 65] This hypothesis is consistent with our findings that a significantly higher percentage of patients in the NoEx were less likely to be employed and reported a lower annual household income.

Consistent with previous studies,[66, 67] compared to the RecEx group, patients in the NoEx group had a higher BMI, a worse comorbidity profile, a higher number of metastatic sites, were more likely to have high blood pressure, diabetes, and back pain, and had a lower functional status. While patients in the RecEx group had a BMI in the normal range, patients in the other two exercise groups had BMIs in the overweight range.[68] In general, studies have found that a higher number of comorbidities is associated with less physical activity.[69, 70] Long-term inactivity and lack of exercise may impair normal organ function and lead to an

increased risk for chronic diseases like hypertension, diabetes, and back pain.[71] While all of these demographic and clinical characteristics associated with being in the LessEx group were reported in studies of the general population, clinicians caring for oncology patients should use this constellation of characteristics to identify high risk patients and initiate appropriate referrals to physical therapists, exercise physiologists, dieticians, and social workers.

As noted in the introduction, findings from several systematic reviews and meta-analyses,[26-34] suggest that multimodal exercise interventions are effective in decreasing fatigue. This study is the first to evaluate the relationships between levels of exercise and self-reports of morning and evening fatigue, as well as decrements in morning and evening energy. None of the previous intervention studies evaluated the effects of exercise on diurnal variations in fatigue severity. In our study, while no differences were found among the exercise groups in the severity of evening fatigue, all of these scores were near the clinically meaningful cutoff score for evening fatigue. In contrast, compared to the other two exercise groups, only the patients in the NoEx group had significantly higher levels of morning fatigue that were above the clinically meaningful cutoff score.

Equally interesting is our findings on the associations between exercise and decrements in energy levels. While most of the literature uses the terms energy and fatigue interchangeably,[72, 73] a growing body of evidence from our group [74, 75] and others [76-78] suggests that energy and fatigue are distinct but related symptoms. In our previous report of characteristics associated with inter-individual differences in the trajectories of morning and evening energy,[74] lack of regular exercise (i.e., dichotomous outcome) was associated with significantly lower levels of morning but not evening energy. However, in the current study, our findings suggest that level of exercise influences decrements in both morning and evening energy. Compared to the RecEx group, patients in the NoEx group had significantly lower levels of evening energy that were below the clinically meaningful cutoff score. While all of the patients in this study had morning energy scores that were below the clinically meaningful cutoff, the

effects of exercise appear to follow a dose response (NoEx < LessEx < RecEx). Taken together with our fatigue findings, future intervention studies should evaluate the effects of exercise on diurnal variations in both fatigue and energy.

While less well studied and often evaluated as a secondary outcome,[35-38] the available evidence suggests that regular exercise results in decreases in sleep disturbance. In our study, all of the exercise groups had scores for the majority of the GSDS subscales, as well as the total score, that were above the clinically meaningful cutoffs. Consistent with the findings from one meta-analysis,[38] patients in the RecEx group reported better sleep quality than the NoEx group. Given the recent interest in evaluating the linkages between fatigue and sleep disturbance in oncology patients in relationship to the efficacy of exercise,[12] one explanation for the low levels of morning energy and high levels of morning fatigue in the NoEx group may be their high levels of self-reported sleep disturbance.

Several limitations need to be acknowledged. Given that exercise was only evaluated at enrollment, we cannot determine causal associations between demographic and clinical characteristics, as well as symptom severity scores, and levels of physical activity. While levels of exercise prior to the initiation of CTX were not evaluated, findings from one study suggest that patients' level of physical activity prior to a cancer diagnosis is a strong predictor of activity up to 10 years post-diagnosis.[79] Given that self-reported levels of exercise, that are susceptible to recall and social desirability biases,[80] were used in this study, future studies should use both subjective and objective measures of physical activity. However, it should be noted that self-reported physical activity is moderately correlated with data obtained using an accelerometer.[81-83]

Despite these limitations, this study provides "real world" evidence of risk factors that clinicians can use to identify patients who are least likely to meet the Office of Disease Prevention and Health Promotion's recommendations for regular exercise.[44] In addition, given that the most frequently used intervention in this sample was walking, clinicians can recommend

this inexpensive exercise to patients to increase their energy levels, as well as decrease fatigue and sleep disturbance. Future studies need to examine the relationships among the dose and types of exercise and these common symptoms in oncology patients, as well as the mechanisms that underlie these inter-relationships.

Please see “Table 1: Differences in Demographic and Clinical Characteristics Among the Exercise Groups” attached.

Please see “Table 2: Differences in Fatigue, Energy, and Sleep Disturbance Scores Among the Exercise Groups” attached.

REFERENCES

1. American, Cancer, and Society, *Cancer Treatment & Survivorship - Facts & Figures 2019-2021*. 2019, American Cancer Society: Atlanta.
2. Ahlberg, K., et al., *Assessment and management of cancer-related fatigue in adults.* The Lancet, 2003. **362**(9384): p. 640-650.
3. Berger, A.M., et al. *NCCN Guidelines Version 1.2020 - Cancer-Related Fatigue*. 2020 02/21/20; Available from: https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf.
4. Saligan, L.N., et al., *The biology of cancer-related fatigue: a review of the literature.* Support Care Cancer, 2015. **23**(8): p. 2461-78.
5. Yang, S., et al., *A Narrative Review of Cancer-Related Fatigue (CRF) and Its Possible Pathogenesis.* Cells, 2019. **8**(7).
6. Thong, M.S.Y., et al., *Cancer-Related Fatigue: Causes and Current Treatment Options.* Curr Treat Options Oncol, 2020. **21**(2): p. 17.
7. Savard, J., et al., *Natural course of insomnia comorbid with cancer: an 18-month longitudinal study.* J Clin Oncol, 2011. **29**(26): p. 3580-6.
8. Savard, J. and C.M. Morin, *Insomnia in the context of cancer: a review of a neglected problem.* J Clin Oncol, 2001. **19**(3): p. 895-908.
9. Palesh, O.G., et al., *Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program.* J Clin Oncol, 2010. **28**(2): p. 292-8.
10. Walker, W.H., 2nd and J.C. Borniger, *Molecular Mechanisms of Cancer-Induced Sleep Disruption.* Int J Mol Sci, 2019. **20**(11).

11. Charalambous, A., et al., *Cancer-related fatigue and sleep deficiency in cancer care continuum: concepts, assessment, clusters, and management.* Support Care Cancer, 2019. **27**(7): p. 2747-2753.

12. Medysky, M.E., et al., *Exercise, sleep and cancer-related fatigue: Are they related?* Neurophysiol Clin, 2017. **47**(2): p. 111-122.

13. Bower, J.E., et al., *Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism?* J Clin Oncol, 2011. **29**(26): p. 3517-22.

14. Dhruva, A., et al., *A longitudinal study of measures of objective and subjective sleep disturbance in patients with breast cancer before, during, and after radiation therapy.* J Pain Symptom Manage, 2012. **44**(2): p. 215-28.

15. Van Onselen, C., et al., *Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer.* J Pain Symptom Manage, 2013. **45**(2): p. 244-60.

16. Mark, S., et al., *Modifiable and non-modifiable characteristics associated with sleep disturbance in oncology outpatients during chemotherapy.* Support Care Cancer, 2017. **25**(8): p. 2485-2494.

17. Dhruva, A., et al., *Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy.* Cancer Nurs, 2010. **33**(3): p. 201-12.

18. Alfaro, E., et al., *Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery.* Eur J Oncol Nurs, 2014. **18**(1): p. 85-93.

19. Miaskowski, C., et al., *Trajectories of fatigue in men with prostate cancer before, during, and after radiation therapy.* J Pain Symptom Manage, 2008. **35**(6): p. 632-43.

20. Wright, F., et al., *Trajectories of Evening Fatigue in Oncology Outpatients Receiving Chemotherapy.* J Pain Symptom Manage, 2015. **50**(2): p. 163-75.

21. Wright, F., et al., *Predictors and Trajectories of Morning Fatigue Are Distinct From Evening Fatigue.* J Pain Symptom Manage, 2015. **50**(2): p. 176-89.

22. Hojman, P., et al., *Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment.* Cell Metab, 2018. **27**(1): p. 10-21.

23. Hojman, P., *Exercise protects from cancer through regulation of immune function and inflammation.* Biochem Soc Trans, 2017. **45**(4): p. 905-11.

24. Stout, N.L., et al., *A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017).* PM R, 2017. **9**(9S2): p. S347-S384.

25. Segal, R., et al., *Exercise for people with cancer: a systematic review.* Curr Oncol, 2017. **24**(4): p. e290-e315.

26. Nadler, M.B., et al., *The Effect of Exercise on Quality of Life, Fatigue, Physical Function, and Safety in Advanced Solid Tumor Cancers: A Meta-analysis of Randomized Control Trials.* J Pain Symptom Manage, 2019. **58**(5): p. 899-908 e7.

27. Kessels, E., O. Husson, and C.M. van der Feltz-Cornelis, *The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis.* Neuropsychiatr Dis Treat, 2018. **14**: p. 479-494.

28. Oberoi, S., et al., *Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis of randomized trials.* Crit Rev Oncol Hematol, 2018. **122**: p. 52-59.

29. Kelley, G.A. and K.S. Kelley, *Exercise and cancer-related fatigue in adults: a systematic review of previous systematic reviews with meta-analyses.* BMC Cancer, 2017. **17**(1): p. 693.

30. Juvet, L.K., et al., *The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: A meta-analysis.* Breast, 2017. **33**: p. 166-177.

31. Dennett, A.M., et al., *Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression.* J Physiother, 2016. **62**(2): p. 68-82.

32. van Vulpen, J.K., et al., *Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: A meta-analysis.* Maturitas, 2016. **85**: p. 104-11.

33. Tian, L., et al., *Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials.* Support Care Cancer, 2016. **24**(2): p. 969-983.

34. Meneses-Echavez, J.F., E. Gonzalez-Jimenez, and R. Ramirez-Velez, *Effects of Supervised Multimodal Exercise Interventions on Cancer-Related Fatigue: Systematic Review and Meta-Analysis of Randomized Controlled Trials.* Biomed Res Int, 2015. **2015**: p. 328636.

35. Matthews, E.E., et al., *Effects of Exercise on Sleep in Women with Breast Cancer: A Systematic Review.* Sleep Med Clin, 2018. **13**(3): p. 395-417.

36. Bernard, P., et al., *Effects and moderators of exercise on sleep in adults with cancer: Individual patient data and aggregated meta-analyses.* J Psychosom Res, 2019. **124**: p. 109746.

37. Mercier, J., J. Savard, and P. Bernard, *Exercise interventions to improve sleep in cancer patients: A systematic review and meta-analysis.* Sleep Med Rev, 2017. **36**: p. 43-56.

38. Fang, Y.Y., et al., *Meta-analysis: Exercise intervention for sleep problems in cancer patients.* Eur J Cancer Care (Engl), 2019. **28**(5): p. e13131.

39. Andrykowski, M.A., A.O. Beacham, and P.B. Jacobsen, *Prospective, longitudinal study of leisure-time exercise in women with early-stage breast cancer.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(3): p. 430-8.

40. Midtgaard, J., et al., *Self-reported physical activity behaviour; exercise motivation and information among Danish adult cancer patients undergoing chemotherapy.* Eur J Oncol Nurs, 2009. **13**(2): p. 116-21.

41. Faul, L.A., et al., *Relationship of exercise to quality of life in cancer patients beginning chemotherapy.* J Pain Symptom Manage, 2011. **41**(5): p. 859-69.

42. Cho, M.H., et al., *Comparisons of exercise dose and symptom severity between exercisers and nonexercisers in women during and after cancer treatment.* J Pain Symptom Manage, 2012. **43**(5): p. 842-54.

43. Gal, R., et al., *Physical activity levels of women with breast cancer during and after treatment, a comparison with the Dutch female population.* Acta Oncologica, 2019. **58**(5): p. 673-681.

44. Office, et al., *Healthy People 2020: Data Search - Physical Activity*. September 13, 2018.

45. Karnofsky, D., *Performance scale*. Factors that influence the therapeutic response in cancer: a comprehensive treatise, ed. G.T. Kennealey and M.S. Mitchell. 1977, New York: Plenum Press.

46. Sangha, O., et al., *The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research.* Arthritis Rheum, 2003. **49**(2): p. 156-63.

47. Lee, K.A., G. Hicks, and G. Nino-Murcia, *Validity and reliability of a scale to assess fatigue.* Psychiatry Res, 1991. **36**(3): p. 291-8.

48. Fletcher, B.S., et al., *Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer.* J Clin Oncol, 2008. **26**(4): p. 599-605.

49. Miaskowski, C. and K.A. Lee, *Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study.* J Pain Symptom Manage, 1999. **17**(5): p. 320-32.

50. Lee, K.A., *Self-reported sleep disturbances in employed women.* Sleep, 1992. **15**(6): p. 493-8.

51. Lee, K.A. and J.F. DeJoseph, *Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women.* Birth, 1992. **19**(4): p. 208-13.

52. United, et al. *Facts & Statistics - Physical Activity*. [cited 2020; Available from: https://www.hhs.gov/fitness/resource-center/facts-and-statistics/index.html.

53. August, K.J. and D.H. Sorkin, *Racial/Ethnic Disparities in Exercise and Dietary Behaviors of Middle-Aged and Older Adults.* Journal of General Internal Medicine, 2011. **26**(3): p. 245-250.

54. Vásquez, E., et al., *Racial and Ethnic Differences in Physical Activity and Bone Density: National Health and Nutrition Examination Survey, 2007–2008.* 2013. **10**.

55. Abraído-Lanza, A.F., M.T. Chao, and K.R. Flórez, *Do healthy behaviors decline with greater acculturation?: Implications for the Latino mortality paradox.* Social Science & Medicine, 2005. **61**(6): p. 1243-1255.

56. Belza, B., et al., *Older adult perspectives on physical activity and exercise: voices from multiple cultures.* Preventing chronic disease, 2004. **1**(4): p. A09-A09.

57. Lee, R.E., C. Cubbin, and M. Winkleby, *Contribution of neighbourhood socioeconomic status and physical activity resources to physical activity among women.* Journal of Epidemiology & Community Health, 2007. **61**(10): p. 882-890.

58. Plonczynski, D.J., *Physical activity determinants of older women: what influences activity?* MEDSURG Nursing, 2003. **12**(4): p. 213-259.

59. Cutler, D. and A. Lleras-Muney, *Education and Health: Evaluating Theories and Evidence*. 2006, National Bureau of Economic Research.

60. Mirowsky, J. and C.E. Ross, *Education, cumulative advantage, and health.* Ageing International, 2005. **30**(1): p. 27-62.

61. Courneya, K.S., et al., *Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy.* Int J Behav Nutr Phys Act, 2014. **11**: p. 85.

62. van Waart, H., et al., *Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy*

Completion Rates: Results of the PACES Randomized Clinical Trial. J Clin Oncol, 2015. **33**(17): p. 1918-27.

63. Witlox, L., et al., *Attendance and compliance with an exercise program during localized breast cancer treatment in a randomized controlled trial: The PACT study.* PLoS One, 2019. **14**(5): p. e0215517.

64. Cutler, D.M. and A. Lleras-Muney, *Understanding differences in health behaviors by education.* Journal of Health Economics, 2010. **29**(1): p. 1-28.

65. Lawrence, E.M., *Why Do College Graduates Behave More Healthfully Than Those Who Are Less Educated?* Journal of Health and Social Behavior, 2017. **58**(3): p. 291-306.

66. Pedersen, B.K. and B. Saltin, *Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases.* Scand J Med Sci Sports, 2015. **25 Suppl 3**: p. 1-72.

67. Roberts, K.C., et al., *Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada.* Health Promot Chronic Dis Prev Can, 2015. **35**(6): p. 87-94.

68. Centers, et al. *About adult BMI, healthy weight*. 2016 May 15, 2015]; Available from: http://www.cdc.gov/healthyweight/assing/bmi/adult_bmi/index.html.

69. Cook, M.J., et al., *The prevalence of co-morbidities and their impact on physical activity in people with inflammatory rheumatic diseases compared with the general population: Results from the UK Biobank.* Rheumatology, 2018. **57**(12): p. 2172-2182.

70. Sievi, N.A., et al., *Impact of comorbidities on physical activity in COPD.* Respirology, 2015. **20**(3): p. 413-418.

71. Booth, F.W., K.C. Roberts, and M.J. Laye, *Lack of exercise is a major cause of chronic diseases.* Comprehensive Physiology, 2012. **2**(2): p. 1143-1211.

72. Gay, C.L., K.A. Lee, and S.Y. Lee, *Sleep patterns and fatigue in new mothers and fathers.* Biol Res Nurs, 2004. **5**(4): p. 311-8.

73. Lee, K.A., et al., *Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics.* J Pain Symptom Manage, 2009. **38**(6): p. 882-93.

74. Abid, H., et al., *Common and Distinct Characteristics Associated With Trajectories of Morning and Evening Energy in Oncology Patients Receiving Chemotherapy.* J Pain Symptom Manage, 2017. **53**(5): p. 887-900 e2.

75. Aouizerat, B.E., et al., *Phenotypic and Molecular Evidence Suggests That Decrements in Morning and Evening Energy Are Distinct but Related Symptoms.* J Pain Symptom Manage, 2015. **50**(5): p. 599-614 e3.

76. Lerdal, A., *A concept analysis of energy. Its meaning in the lives of three individuals with chronic illness.* Scand J Caring Sci, 1998. **12**(1): p. 3-10.

77. Lerdal, A., *A theoretical extension of the concept of energy through an empirical study.* Scand J Caring Sci, 2002. **16**(2): p. 197-206.

78. Lerdal, A., et al., *Development of a short version of the Lee Visual Analogue Fatigue Scale in a sample of women with HIV/AIDS: a Rasch analysis application.* Qual Life Res, 2013. **22**(6): p. 1467-72.

79. Mason, C., et al., *Long-term physical activity trends in breast cancer survivors.* Cancer Epidemiol Biomarkers Prev, 2013. **22**(6): p. 1153-61.

80. Brenner, P.S. and J. DeLamater, *Lies, Damned Lies, and Survey Self-Reports? Identity as a Cause of Measurement Bias.* Soc Psychol Q, 2016. **79**(4): p. 333-354.

81. Sloane, R., et al., *Comparing the 7-day physical activity recall with a triaxial accelerometer for measuring time in exercise.* Med Sci Sports Exerc, 2009. **41**(6): p. 1334-40.

82. Limb, E.S., et al., *Measuring change in trials of physical activity interventions: a comparison of self-report questionnaire and accelerometry within the PACE-UP trial.* Int J Behav Nutr Phys Act, 2019. **16**(1): p. 10.

83. Nelson, S.H., et al., *Physical Activity Change in an RCT: Comparison of Measurement Methods.* Am J Health Behav, 2019. **43**(3): p. 543-555.

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